



Patents 

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )

**JUAN LEGARDA IBANEZ** )

Serial No. **10/622,068** )

Art Unit: 1614

Filed: **July 15, 2003** )

Examiner: Unknown

For: **Use Of Flumazenil in the  
Production of a Medicament for  
the Treatment of Cocaine Dependency** )

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**

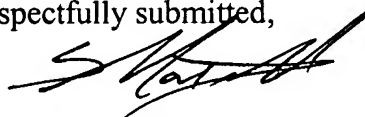
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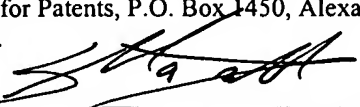
Respectfully submitted,



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**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**

(use as many sheets as necessary)

**Complete if Known**

<b>Application Number</b>	10/622,068
<b>Filing Date</b>	July 15, 2003
<b>First Named Inventor</b>	Juan Legarda Ibanez
<b>Group Art Unit</b>	1614
<b>Examiner Name</b>	Not yet assigned
<b>Attorney Docket Number</b>	55979-314570 (55979-0200)

Sheet	1	of	5
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## U.S. PATENT DOCUMENTS

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## FOREIGN PATENT DOCUMENTS

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**Examiner  
Signature**

Date  
Considered

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Substitute for Form 1449/A/PTO  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> (use as many sheets as necessary)		<b>Complete if Known</b>	
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Sheet 2	of 5	Attorney Docket Number	55979-314570 (55979-0200)

OTHER INFORMATION - NON PATENT LITERATURE DOCUMENTS			
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	3.	Baldwin, H.A., <i>et al.</i> , "Flumazenil Prevents the Development of Chlordiazepoxide Withdrawal in Rats Tested in the Social Interaction Test of Anxiety," <i>Psychopharmacology</i> , Vol. 97, No. 3, pp. 424-426 (1989) (Abstract Only)	
	4.	Brooks-Kayal-A.R., <i>et al.</i> , "Human Neuronal $\gamma$ -Aminobutyric Acid <sub>A</sub> Receptors: Coordinated Subunit mRNA Expression and Functional Correlates in Individual Dentate Granule Cells," <i>J. Neuroscience</i> , Vol. 19, No. 19, pp. 8312-8318 (1999)	
	5.	Criswell, H.E., <i>et al.</i> , "Effect of Zolpidem on Gamma-aminobutyric Acid (GABA)-Induced Inhibition Predicts the Interaction of Ethanol with GABA on Individual Neurons in Several Rat Brain Regions," <i>J. Pharmacol. Exp. Therp.</i> , Vol. 273, No. 1, pp. 526-536 (1995) (Abstract Only)	
	6.	Ferrara, G., <i>et al.</i> , "Increased Expression of the Neuropeptide Y receptor Y1 Gene in the Medical Amygdala of Transgenic Mice Induced by Long-term Treatment with Progesterone or Allopregnanolone," <i>J. Neurochemistry</i> , Vol. 79, pp. 417-425 (2001)	
	7.	Frostholm, A., <i>et al.</i> , "Harmaline-induced Changes in Gamma Aminobutyric Acid <sub>A</sub> Receptor Subunit mRNA Expression in Murine Olivocerebellar Nuclei," <i>Molecular Brain Research</i> , Vol. 85, pp. 200-208 (2000)	
	8.	Gee, K., <i>et al.</i> , "A Putative Receptor for Neurosteroids on the GABA <sub>A</sub> Receptor Complex: The Pharmacological Properties and Therapeutic Potential of Epalons," <i>Crit. Rev. Neurobiol.</i> , Vol. 9, Nos. 2-3, pp. 207-227 (1995)	
	9.	Gulinello, M., <i>et al.</i> , "Progesterone Withdrawal Increases the $\alpha$ 4 Subunit of the GABA <sub>A</sub> Receptor in Male Rats in Association With Anxiety and Altered Pharmacology - A Comparison With Female Rats," <i>Neuropharmacology</i> , Vol. 43, pp. 701-714 (2000)	
	10.	Gulinello, M., <i>et al.</i> , "Anxiogenic Effects of Neurosteroid Exposure: Sex Differences and Altered GABA <sub>A</sub> Receptor Pharmacology in Adult Rats," <i>J. Pharmacology and Experimental Therapeutics</i> , Vol. 305, No. 2, pp. 541-548 (2003)	
	11.	Hawkinson, J.E., "Substituted 3 $\beta$ -Phenylethynyl Derivatives of 3 $\alpha$ -Hydroxy-5 $\alpha$ -pregnan-20-one: Remarkably Potent Neuroactive Steroid Modulators of $\gamma$ -Aminobutyric Acid <sub>A</sub> Receptors," <i>J. Pharmacology and Experimental Therapeutics</i> , Vol. 287, No. 1, p. 198-207 (1998)	
	12.	Hogenkamp, D.J., <i>et al.</i> , "Synthesis and in Vitro Activity of 3 $\beta$ -Substituted-3 $\alpha$ -Hydroxypregnan-20-ones: Allosteric Modulators of the GABA <sub>A</sub> Receptor," <i>J. Med. Chem.</i> , Vol. 40, pp. 61-72 (1996)	
	13.	Hsu, F., <i>et al.</i> , "Progesterone Withdrawal Reduces Paired-Pulse Inhibition in Rate Hippocampus: Dependence on GABA <sub>A</sub> Receptor $\alpha$ 4 Subunit Upregulation," <i>J. Neurophysiol.</i> , Vol. 89, pp. 186-198 (2003)	

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		First Named Inventor	Juan Legarda Ibanez		
		Group Art Unit	1614		
		Examiner Name	Not yet assigned		
Sheet	3	of	5	Attorney Docket Number	55979-314570 (55979-0200)

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	14.	Krogsgaard-Larsen, P., <i>et al.</i> , "GABA <sub>A</sub> Agonists and Partial Agonists: THIP (Gaboxadol) as a Non-Opioid Analgesic and a Novel Type of Hypnotic," <i>Biochemical Pharmacology</i> , Vol. 68, pp. 1573-1580 (2004)	
	15.	Holt, R.A., <i>et al.</i> , "Chronic Treatment with Diazepam or Abecarnil Differently Affects the Expression of GABA <sub>A</sub> Receptor Subunit mRNAs in the Rat Cortex," <i>Neuropharmacology</i> , Vol. 35, Nos. 9 & 10, pp. 1457-1463 (1996)	
	16.	Lan, N.C., <i>et al.</i> , "Differential Responses of Expressed Recombinant Human Gamma-aminobutyric acid <sub>A</sub> Receptors to Neurosteroids," <i>J. Neurochem.</i> , Vol. 57, No. 5, pp. 1818-1821 (1991) (Abstract Only)	
	17.	Lee, C., <i>et al.</i> , "Effects of Benzodiazepine Receptor Antagonist, Flumazenil, on Antinociceptive and Behavioural Responses to the Elevated Plusmaze in Mice," <i>Neuropharmacology</i> , Vol. 30, No. 12A, pp. 1263-1267 (1991) (Abstract Only)	
	18.	Medina, J.H., <i>et al.</i> , "Overview-Flavonoids: A New Family of Benzodiazepine Receptor Ligands," <i>Neurochemical Research</i> , Vol. 22, No. 4, pp. 419-425 (1997)	
	19.	Smith, S.S., <i>et al.</i> , "Neurosteroid Administration and Withdrawal Alter GABA <sub>A</sub> Receptor Kinetics in CA1 Hippocampus of Female Rats," <i>J. Physiol.</i> , Vol. 567, Pt. 2, pp. 421-436 (2005) (Abstract Only)	
	20.	Sur, C., <i>et al.</i> , "Preferential Coassembly of $\alpha 4$ and $\delta$ Subunits of the $\gamma$ -Aminobutyric Acid <sub>A</sub> Receptor in Rat Thalamus," <i>American Society of Pharmacology and Experimental Therapeutics</i> , Vol. 56, pp. 110-115 (1998)	
	21.	Van Miert, A.S., <i>et al.</i> , "Appetite-modulating Drugs in Dwarf Goats, With Special Emphasis on Benzodiazepine-induced Hyperphagia and Its Antagonism by Flumazenil and RO 15-3505," <i>J. Vet. Pharmacol. Ther.</i> , Vol. 12, No. 2, pp. 147-156 (1989)	
	22.	Whittemore, E.R., <i>et al.</i> , "Pharmacology of the Human Gamma-aminobutyric acid <sub>A</sub> Receptor Alpha 4 Subunit Expressed in <i>Xenopus</i> Laevis Oocytes," <i>Mol. Pharmacol.</i> , Vol. 50, No. 5, pp. 1364-1375 (1996) (Abstract Only)	
	23.	Wisden, W., <i>et al.</i> , "Cloning, Pharmacological Characteristics and Expression Pattern of the Rat GABA <sub>A</sub> Receptor Alpha 4 Subunit," <i>FEBS Lett.</i> , Vol. 289, No. 2, pp. 227-230 (1991) (Abstract Only)	

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	24.	Adkins, C.E., <i>et al.</i> , "α4β3δ GABA <sub>A</sub> Receptors Characterized by Fluorescence Resonance Energy Transfer-derived Measurements of Membrane Potential," <i>J. Biological Chemistry</i> , Vol. 276, No. 42, pp. 38934-38939 (2001)	
	25.	Akk, G., <i>et al.</i> , "Activation of GABA(A) Receptors Containing the alpha4 subunit by GABA and Pentobarbital," <i>J. Physiol.</i> , Vol. 556, Part 2, , pp. 387-399 (2004)	
	26.	Banerjee, P.K., <i>et al.</i> , "Alterations in GABA <sub>A</sub> Receptor α1 and α4 Subunit mRNA Levels in Thalamic Relay Nuclei Following Absence-like Seizures in Rats," <i>Experimental Neurology</i> , Vol. 154, pp. 213-223 (1998)	
	27.	Biggio, G., <i>et al.</i> , "GABA <sub>A</sub> -receptor Plasticity During Long-Term Exposure to and Withdrawal from Progesterone," <i>Int. Rev. Neurobiol.</i> , Vol. 46, pp. 207-241 (2001)	
	28.	Burt, D.R., "Alpha Subunit Position and GABA Receptor Function," <i>Science's STKE</i> , No. 270, PE5, pp. 1-2 (2005)	
	29.	Lovick, T.A., <i>et al.</i> , "Changes in GABA <sub>A</sub> Receptor Subunit Expression in the Midbrain During the Oestrous Cycle in Wistar Rats," <i>Neuroscience</i> , Vol. 131, pp. 397-405 (2005)	
	30.	Lujan, R., <i>et al.</i> , "Glutamate and GABA Receptor Signalling in the Developing Brain," <i>Neuroscience</i> , Vol. 130, pp. 567-580 (2005)	
	31.	Mody, I., "Distinguishing between GABA <sub>A</sub> Receptors Responsible for Tonic and Phasic Conductances," <i>Neurochemical Research</i> , Vol. 26, Nos. 8-9, pp. 907-913 (2001)	
	32.	Porter, B.E., <i>et al.</i> , "Heterogeneous GABA(A) Receptor Subunit Expression in Pediatric Epilepsy Patients," <i>Neurobiol. Dis.</i> , Vol. 18, No. 3, pp. 484-491 (2005) (Abstract Only)	
	33.	Quirk, G.J., <i>et al.</i> , "Inhibition of the Amygdala: Key to Pathological States?," <i>Ann. N.Y. Acad. Sci.</i> , Vol. 985, pp. 263-272 (2003)	
	34.	Rissman, R.A., <i>et al.</i> , "Subregional Analysis of GABA <sub>A</sub> Receptor Subunit mRNAs in the Hippocampus of Older Persons with and without Cognitive Impairment," <i>J. Chemical Neuroanatomy</i> , Vol. 28, pp. 17-25 (2004)	
	35.	Saitoh, K., <i>et al.</i> , "Nigral GABAergic Inhibition Upon Mesencephalic Dopaminergic Cell Groups in Rats," <i>Eur. J. Neurosci.</i> , Vol. 19, No. 9, pp. 2399-2409 (2004) (Abstract Only)	
	36.	Sedvall, G., <i>et al.</i> , "Recent Advances in Psychiatric Brain Imaging," <i>Acta Radiol.Suppl.</i> , Vol. 374, pp. 113-115 (1990) (Abstract Only)	

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	37.	Smith, A.J., <i>et al.</i> , "Effect of a Subunit on Allosteric Modulation of Ion Channel Function in Stably Expressed Human Recombinant $\gamma$ -Aminobutyric Acid <sub>A</sub> Receptors Determined Using <sup>36</sup> Cl Ion Flux," <i>Molecular Pharmacology</i> , Vol. 59, No. 5, pp. 1108-1118 (2001)	
	38.	Smith, S.S., <i>et al.</i> , "GABA <sub>A</sub> Receptor $\alpha$ 4 Subunit Suppression Prevents Withdrawal Properties of an Endogenous Steroid," <i>Nature</i> , Vol. 392, pp. 926-930 (1998)	
	39.	Weinbroum, A.A., <i>et al.</i> , "Flumazenil Potentiation of Postoperative Morphine Analgesia," <i>Clin J. Pain</i> , Vol. 16, No. 3, pp. 193-199 (2000) (Abstract Only)	
	40.	White, J.A., <i>et al.</i> , "Antagonism of a Nicotine Plus Midazolam Discriminative Cue in Rats," <i>Behav. Pharmacol.</i> , Vol. 5, No. 3, pp. 361-355 (1994) (Abstract Only)	
	41.	Yang, W., "Cloning and Characterization of the Human GABA <sub>A</sub> Receptor Alpha 4 Subunit: Identification of a Unique Diazepam-Insensitive Binding Site," <i>Eur. J. Pharmacol.</i> , Vol. 291, No. 3, pp. 319-325 (1995) (Abstract Only)	
	42.	Zheng, T.M., <i>et al.</i> , "Chronic Flumazenil Alters GABA <sub>A</sub> Receptor Subunit mRNA Expression, Translation Product Assembly and Channel Function in Neuronal Cultures," <i>J. Pharmacol. Exp. Ther.</i> , Vol. 277, No. 1, pp. 525-533 (1996) (Abstract Only)	
	43.	Zheng, T.M., <i>et al.</i> , "Changes in $\gamma$ -aminobutyrate Type A Receptor Subunit mRNAs, Translation Product Expression, and Receptor Function During Neuronal Maturation in vitro," <i>Proc. Natl. Acad. Sci. USA</i> , Vol. 91, pp. 10952-10956 (1994)	

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